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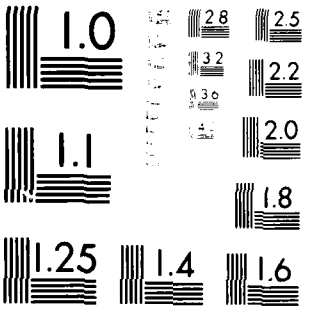

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PRIMATE EQUILIBRIUM PERFORMANCE AND DIAZEPAM: A BEHAVIORAL TOLERANCE EFFECT

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NOTICES

This final report was submitted by Systems Research Laboratories, Inc., 2800 Indian Ripple Road, Dayton, Ohio 45440-3696, under contract F33615-80-C-0603, job order 7757-05-43, with the USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks Air Force Base, Texas. Captain Thomas E. Dayton (USAFSAM/RZV) was the Laboratory Project Scientist-in-Charge.

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The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources - National Research Council.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

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Well-trained rhesus macaques were tested for their ability to perform a compensatory tracking task (Primate Equilibrium Platform) under the influence of diazepam. Performance decrements were observed that depended not only on the dose, but also on the amount of prior experience of the animal with the drug. Such tolerance effects make it inappropriate to use repeated measures designs to derive dose-effects functions for performance. The impact of tolerance effects on the measurement and interpretation of drug-induced performance decrements was discussed.

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PRIMATE EQUILIBRIUM PERFORMANCE AND DIAZEPAM: A BEHAVIORAL TOLERANCE EFFECT

INTRODUCTION

Diazepam has been proposed as part of the therapeutic regimen for organophosphate intoxication in military personnel. While a wealth of data on diazepam effects in man exists, there are no data on its effects in combination with low doses of nerve agents. Data on the effects of nerve agents and diazepam in combination would be useful in assessing the ability of personnel to perform their duties following exposure and treatment. Since human subjects cannot be used for such combined effects studies, the rhesus monkey is used as a model.

The present study of the effects of diazepam on performance by monkeys was preliminary to a combined diazepam-agent study. Primate Equilibrium Performance (PEP), a compensatory tracking task, was chosen as a behavioral model of aspects of pilot performance (1). Since no prior data on the effects of diazepam on performance of a compensatory tracking task by monkeys existed, it was first necessary to determine the dose-range of interest. Based on results from other tasks, i.e., delayed alternation (8), diazepam doses of 0 (saline control), 0.05, 0.10, and 0.15 mg/kg were selected initially.

The experiment was designed using repeated measures, with each animal to receive all doses in random order. The validity of this design depends on the assumption that no effects carry over from dose to dose. To minimize carry-over effects, the minimum interval between doses was 10 days. The animals were always tested between doses to verify that their performance had returned to a normal baseline. In order to increase the efficiency of the experimental design, it was desirable to exclude doses of diazepam that were either too low to produce a measurable effect or too high to permit measurement (i.e., totally incapacitating). The first animal injected was one scheduled to receive the placebo as his first treatment. The next animal injected was one scheduled to receive the lowest dose (0.05 mg/kg) first in his treatment series. The third animal tested received an initial injection of 0.10 mg/kg, and the fourth animal received an initial injection of 0.15 mg/kg.

When these doses failed to produce any obvious performance effect, higher doses (0.20 - 0.60 mg/kg) were injected, in order to establish the dose-range of interest. After this was accomplished, a new dose schedule could be constructed.

METHODS AND PROCEDURES

The PEP and methods and procedures for its use have been described in detail previously (1). The 6 animals in the present study performed the PEP compensatory tracking task for 20 consecutive 5-min epochs. The task for each animal (adult Macaca mulatta, 7 - 10 kg) was to move a control stick in such a way as to compensate for random perturbations in the position of the platform on which it was seated. The position of the platform was measured 10 times per second and the quality of the tracking performance was measured by the root mean squared (RMS) variation in platform position. On treatment days, testing was interrupted briefly after the sixth epoch, when the animal received the scheduled drug or placebo injection intramuscularly in the lateral aspect of the thigh. Testing was resumed immediately after the injection. Thus, data were recorded for 30 min before and 70 min after injection. Animals were tested in pairs, always at the same time of day (between 0700 and 0900 for some pairs, between 0900 and 1100 for others).

RESULTS

During the dose-ranging phase of this study, we observed that doses between 0.35 and 0.60 mg/kg produced extremely variable performance effects. Paradoxically, doses near the high end of this range frequently produced smaller effects than doses near the low end.

As a consequence of the way our exploratory sequence of doses was given to the sequence of available monkeys, some monkeys received moderate doses (0.35 - 0.50 mg/kg) as their first or second exposure to the drug. On the other hand, higher (0.45 - 0.60 mg/kg) doses typically were given to a monkey only after he had previously experienced several lower doses. An examination of the effects relative to the dosage history of each animal suggested that the paradoxical results might be explained by the development of a tolerance to the drug. Drug tolerance, in the chronic sense, refers to the fact that a history of exposure to a drug leads to a condition in which a greater dose is required to produce the same effect, or a constant dose produces a reduced effect.

If PEP performance shows tolerance with respect to diazepam, the original (repeated measures) design of our experiment would be invalidated, since tolerance is a carry-over effect from early to later doses. Therefore, it was important to test the tolerance hypothesis. So, a series of further doses was scheduled to accomplish two comparisons: early vs. late exposure to similar doses, and a gradual buildup to even higher doses (in animals that had already experienced a gradual buildup to moderate

doses). Figure 1 presents examples of these two comparisons. In the upper half of the figure, the performance decrement produced by a diazepam dose of 0.425 mg/kg with no prior experience is compared to the effect on the same animal of a 0.45 mg/kg dose after experience with 3 prior injections (0.425 mg/kg, 0.50 mg/kg, and 0.35 mg/kg). The data from control runs demonstrates the stability of the performance baseline in these well practiced subjects. It is apparent that the performance decrement produced by the 0.45 mg/kg dose is less than what would be predicted from the effect of the earlier 0.425 mg/kg dose. This implies that the dose-effect function for diazepam changed between the first and fourth injection.

The lower half of Figure 1 compares the performance decrement due to a 0.45 mg/kg initial dose with the decrement produced by 0.80 mg/kg after a series of increasing doses in another animal. Here, the effect of a high dose late in the series is clearly less than that of a moderate dose at the beginning. Again, this implies a change in the dose-effect function concomitant with repeated exposures to diazepam.

DISCUSSION

The original goal of this experiment was to measure a dose-effects function for the effects of diazepam on performance of the PEP compensatory tracking task. The results show that the amount of performance decrement is not only a function of dose, but also depends on prior experience with the drug. This finding implies that a family of dose-effect functions exists, falling between relatively severe effects on first exposure and much milder effects after many exposures (assuming that the extent of tolerance reaches some asymptotic level). In other words, a given dose of diazepam produces the greatest performance decrement on first exposure and smaller decrements as prior experience with the drug increases. Thus, a dose-effects function based on data from initial exposures would show effects at lower doses and rise more steeply than a function based on data gathered from subjects experienced with the drug. The extremes of this family of dose-effect functions could be explored by employing two distinct experimental strategies:

1. Measurement of the effects on initial exposure would require using an independent group of well-trained subjects for each dose in the range of interest.

2. Measurement of the effects at asymptotic tolerance could be accomplished using a repeated measures design after each subject had been exposed to all doses in the range of interest repeatedly, so that no further change in performance occurred with repeated exposure to each dose.

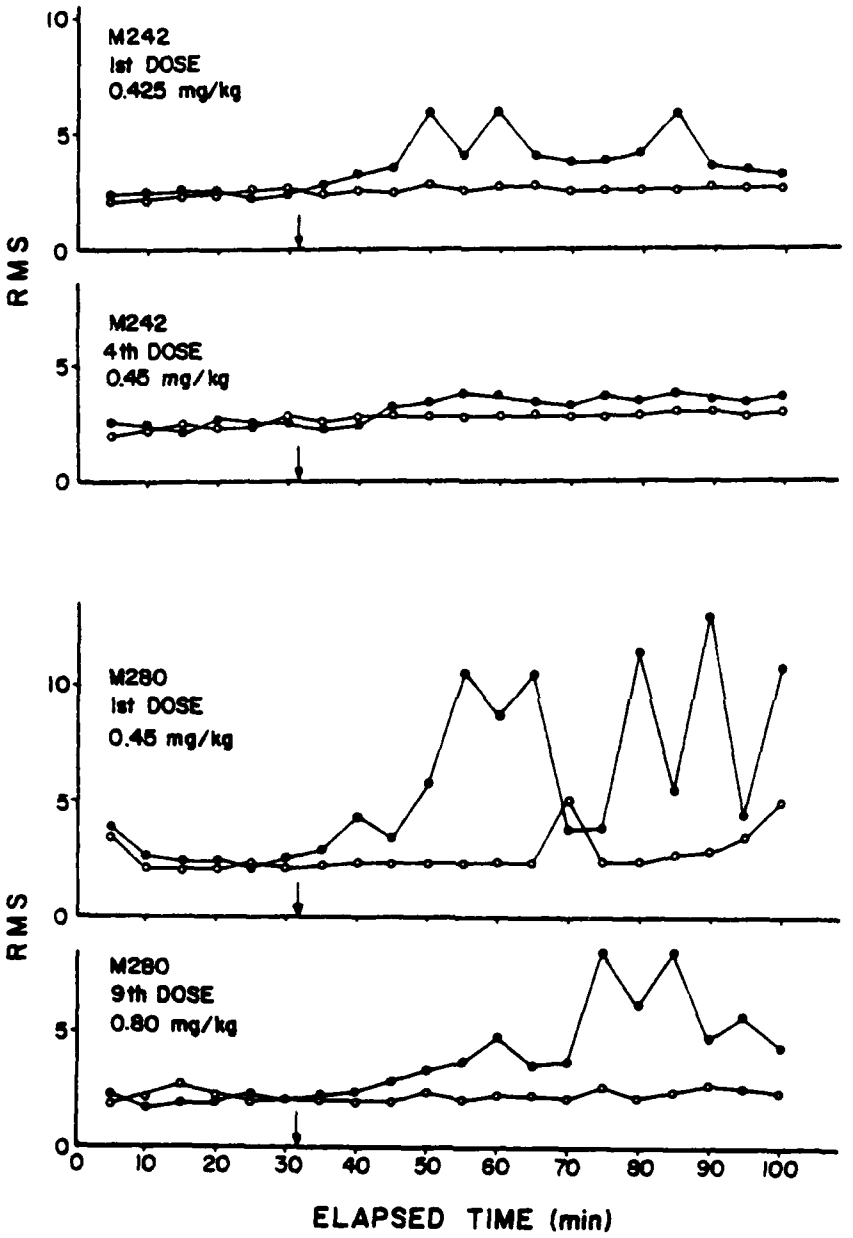

Figure 1. A comparison in 2 monkeys of the performance effects of initial exposure to diazepam with the effects of similar or larger doses administered after prior experience with diazepam. Time of injection is indicated by the arrow on the abscissa. Injections: Filled circles indicate diazepam; open circles indicate placebo.

Obviously, both of these strategies require the use of resources much more extensive than those contemplated in the original design of this study.

The results of this study indicate that diazepam, like other psychoactive drugs that have been examined (e.g., opiates, cholinergics, alcohol, marijuana, and a variety of "anxiolytic" drugs), produces behavioral tolerance effects (2, 3, 4, 5, 6, 8). Behavioral tolerance is distinguished from physiologic tolerance by the fact that drug-induced decrements in behavior dissipate more rapidly than the drug is cleared from the system; or, on repeated exposures, by the fact that equal circulating levels of drug produce smaller behavioral decrements as experience with the drug increases. Also, during periods of drug abstinence, physiologic tolerance tends to dissipate more rapidly than does behavioral tolerance. Since circulating levels of diazepam and its active metabolites were not measured in the current experiment, a distinction between physiologic and behavioral tolerance must be viewed with caution. However, after intervals of 8 to 10 weeks with no drug exposure, the tolerance effects reported here were still observed, which supports the interpretation of these effects as a behavioral tolerance.

The existence of behavioral tolerance effects has significance both for the experimental design and for the operational interpretation of drug-performance studies. Future studies of the performance effects of psychoactive drugs should adopt one of the two strategies outlined above, depending on the situation to which experimenters wish to generalize their results. For mission survivability/vulnerability studies, the first-exposure strategy (strategy 1) will typically provide information for a "worst-case" analysis, since most psychoactive drugs produce the largest performance decrements on first exposure. The asymptotic tolerance strategy (strategy 2) is appropriate for drugs (e.g., alcohol) that may be in common use in the population of interest. However, it should be noted that this strategy provides "best-case" data. That is, the dose-response function derived from subjects with a well-developed tolerance will show less severe effects than would be expected, on average, from a general population.

Our results further suggest that rhesus macaques are less susceptible than humans to the deleterious effects of diazepam on a tracking task. O'Hanlon et al (9) have shown significant impairments of lateral position control in highway driving in humans at oral doses of 0.15 mg/kg or less (10 mg doses in adult males, weight not given), a dose much lower than the effective dose that we observed in monkeys. The effective dose in monkeys, delivered intramuscularly, would have produced blood levels 5 to 10 times higher than the oral dose which impaired driving ability in human subjects.

SUMMARY

Well-trained rhesus macaques were tested for their ability to perform a compensatory tracking task (Primate Equilibrium Platform) under the influence of diazepam. Performance decrements were observed that depended not only on the dose, but also on the amount of prior experience of the animal with the drug. Such tolerance effects make it inappropriate to use repeated measures designs to derive dose-effects functions for performance. The impact of tolerance effects on the measurement and interpretation of drug-induced performance decrements was discussed.

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